U.S. Application No.: 09/985,699
Amendment dated November 29, 2004
In Reply to the Office Action of November 28, 2003
Attorney Ref. No.: 068800-0284057

I. AMENDMENT

Amendments to the Claims

This listing of claims will replace all prior versions, and listings, of claims in the application.

Claims 1-17 are canceled, claims 18-35 are amended, and new claims 36-39 are added.

1-17. (Canceled)

18. (Currently amended) A ~~Method~~ method for the depletion of ~~an unwanted~~ a disease-associated protein population from the plasma of a subject in need of such treatment, which comprises:

(a) administering to the subject a therapeutically effective amount of a non-proteinaceous agent, which agent comprises a plurality of ligands covalently co-linked ~~so as to form a~~ to permit complexation with a plurality of the disease-associated proteins in the presence thereof, wherein at least two of the ligands are the same or different and are capable of being bound by ligand binding sites present on the proteins;

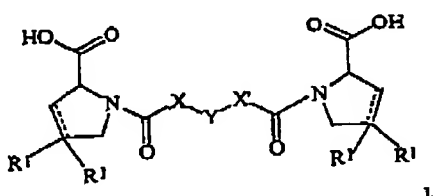
(b) binding of at least two of the ligands by the ligand binding sites of the proteins in the plasma;

(c) forming thereby a complex between the agent and a plurality of the proteins, wherein the complex is abnormal to the subject; and

(d) causing the complex to be identified by the physiological mechanisms of the subject and cleared from the plasma; and

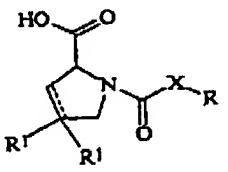
(e) monitoring the clearance of the disease-associated protein population from the subject's plasma.

19. (Currently amended) The ~~Method~~ method according to claim 18, wherein the agent is a D-proline of the formula



I-A

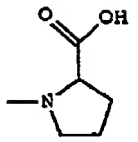
or



I-B

wherein

R is the group



;

R^1 is hydrogen or halogen;

X is- $(CH_2)_n$-; $-CH(R^2)(CH_2)_n$-; $-CH_2O(CH_2)_n$-; $-CH_2NH$-; benzyl, $-C(R^{2)}=CH$-; $-CH_2CH(OH)$-; or thiazol-2,5-diyl;

Y is -S-S-; $-(CH_2)_n$-; -O-; -NH-; $-N(R^2)$-; -CH=CH-; -NHC(O)NH-; $-N(R^2)C(O)N(R^2)$-; $-N[CH_2C_6H_3(OCH_3)_2]$-; $-N(CH_2C_6H_5)$-; $-N(CH_2C_6H_5)C(O)N(CH_2C_6H_5)$-; -N(alkoxyalkyl)-; N(cycloalkyl-methyl)-; 2,6-pyridyl; 2,5-furanyl; 2,5-thienyl; 1,2-cyclohexyl; 1,3-cyclohexyl; 1,4-cyclohexyl; 1,2-naphthyl; 1,4-naphthyl; 1,5-naphthyl; 1,6-naphthyl; biphenylen; or 1,2-phenylen, 1,3-phenylen and 1,4-phenylen, wherein the phenylen groups are optionally substituted by 1 - 4 substituents, selected from halogen, lower alkyl, lower alkoxy, hydroxy, carboxy, -COO-lower alkyl, nitrilo, 5-tetrazol, (2-carboxylic acid pyrrolidin-1-yl)-2-oxo-ethoxy, N-hydroxycarbamimidoyl, 5-oxo[1,2,4]oxadiazolyl, 2-oxo-[1,2,3,5] oxathiadiazolyl, 5-thioxo[1,2,4]oxadiazolyl and 5-tert-butylsulfanyl-[1,2,4] oxadiazolyl;

X' is $-(CH2)_n$-; $-(CH_2)_nCH(R^2)$-; $-(CH_2)_nOCH_2$-; $-NHCH_2$-; benzyl, $-CH=C(R^2)$-; $-CH(OH)CH^2$; or thiazol-2,5-diyl;

R^2 is lower alkyl, lower alkoxy or benzyl and

n is 0-3,

or a pharmaceutically acceptable salt or mono- or diester thereof.

20. (Currently amended) The ~~Method~~ method according to claim 19, wherein the D-proline is (R)-1-[6-(R)-2-Carboxypyrrolidin-1-yl]-6-oxo-hexanoyl] pyrrolidine-2-carboxylic acid or a pharmaceutically acceptable salt or mono- or diester thereof.

21. (Currently amended) The ~~Method~~ method according to claim 18, wherein the ligands are covalently co-linked in the agent by a linker.

22. (Currently amended) The ~~Method~~ method according to claim 21, wherein the linker comprises a linear or branched hydrocarbylene in which one or more of the carbon atoms thereof is optionally substituted by a heteroatom.

23. (Currently amended) The ~~Method~~ method according to claim 18, wherein the agent has two ligands.

24. (Currently amended) A ~~Method~~ method for the depletion of ~~an unwanted~~ a disease-associated protein population from the plasma of a subject in need of such treatment, which comprises administering to the subject a therapeutically effective amount of a non-proteinaceous agent, which agent has the general structure Ligand-linker-Ligand and is capable of forming a complex with a plurality of the disease-associated proteins in the presence thereof, wherein the ligands are the same or different and are capable of being bound by ligand binding sites present on the proteins; and monitoring the clearance of the disease-associated protein population from the subject's plasma.

25. (Currently amended) The ~~Method~~ method according to claim 18, wherein each ligand in the agent is selected to be specific for an individual target protein, and to be bound by the protein with a dissociation constant which is no more than 1 millimolar.

26. (Currently amended) A ~~Method~~ method for the depletion of ~~an unwanted~~ a disease-associated protein population from the plasma of a subject in need of such treatment, which comprises administering to the subject a therapeutically effective amount of a non-proteinaceous agent, which agent comprises a plurality of ligands covalently co-linked so as to form a complex with a plurality of the disease-associated proteins in the presence thereof, wherein at least two of the ligands are the same or different and are capable of being bound by ligand binding sites present on one or more proteins selected from a normal or abnormal, variant, protein of any of the following types: cytokine, lipoprotein, autoantibody, acute phase protein, amyloidogenic protein, complement protein, ~~or~~ and coagulation protein;

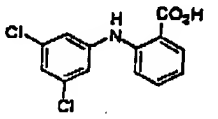
and monitoring the clearance of the disease-associated protein population from the subject's plasma.

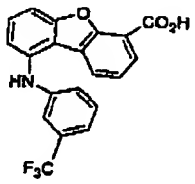
27. (Currently amended) The ~~Method~~ method according to claim 26, wherein the ligand binding site is from an acute phase protein comprising serum amyloid A protein (SAA).

28. (Currently amended) The ~~Method~~ method according to claim 26, wherein the ligand binding site is from serum amyloid P component (SAP).

29. (Currently amended) The ~~Method~~ method according to claim ~~27~~ 26, wherein the ligand binding site is from an amyloidogenic protein ~~comprising~~ selected from the group consisting of a monoclonal immunoglobulin light chain, transthyretin, β_2-microglobulin ~~or~~ and lysozyme.

30. (Currently amended) The ~~Method~~ method according to claim 29, wherein the ligand binding site is from transthyretin and at least one of the ligands comprises





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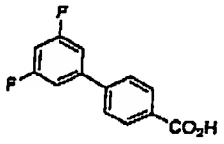

31. (Currently amended) The ~~Method~~ method according to claim 29, wherein the ligand binding site is from lysozyme and at least one of the ligands comprises a disaccharide

or oligosaccharide analogue ~~containing at least~~ comprising N-acetylmuramic acid ~~linked via its C1 atom to the C4 atom of, for example, N-acetyl glucosamine, with the O atom of the 1,4 β glycosidic linkage replaced by a carbon or other non-O atom~~.

32. (Currently amended) The ~~Method~~ method according to claim 26, wherein the ligand binding site is from an autoantibody and at least one of the ligands comprises an epitope to which the autoantibody is specific.

33. (Currently amended) The ~~Method~~ method according to claim 18 wherein each ligand of the agent is capable of binding to the same ligand binding site.

34. (Currently amended) The ~~Method~~ method according to claim 18, wherein at least two ligands of the agent are different from one another and are capable of being bound by different proteins.

35. (Currently amended) The ~~Method~~ method according to claim 34, wherein one of the ligands of the agent is capable of being bound by SAP.

New claims:

36. (New) The method according to claim 31, wherein the N-acetylmuramic acid is linked to N-acetylglucosamine by a modified 1,4 β glycosidic linkage, the O atom of which is replaced by a non-O atom.

37. (New) The method according to claim 36, wherein the O atom is replaced by carbon.

38. (New) The method according to claim 36, wherein the O atom is replaced by a non-O atom that can enable hydrogen bonding contributed by the replaced oxygen.

39. (New) The method according to claim 38, wherein the O atom is replaced by nitrogen or fluorine.

40. (New) The method according to claim 18, comprising clearing from the subject's plasma one or more disease-associated proteins that are normal or abnormal, variant, proteins selected from any of the following types: cytokine, lipoprotein, autoantibody, acute phase protein, amyloidogenic protein, complement protein, and coagulation protein.

41. (New) The method according to claim 40, wherein the disease-associated protein is serum amyloid A protein (SAA).

42. (New) The method according to claim 40, wherein the disease-associated protein is serum amyloid P component (SAP).

43. (New) The method according to claim 40, wherein the disease-associated protein is an amyloidogenic protein selected from the group consisting of a monoclonal immunoglobulin light chain, transthyretin, β_2-microglobulin and lysozyme.

44. (New) A method for the depletion of disease-associated proteins from the plasma of a subject in need of such treatment, which comprises:

administering to the subject a therapeutically effective amount of a non-proteinaceous agent, which agent comprises a plurality of ligands covalently co-linked to permit complexation with a plurality of the disease-associated proteins in the presence thereof, wherein at least two of the ligands are the same or different and are capable of being bound by ligand binding sites present on the proteins; and

monitoring the clearance of the disease-associated proteins from the subject's plasma;

wherein the disease-associated proteins are one or more normal or abnormal, variant, proteins selected from any of the following types: cytokine, lipoprotein, autoantibody, acute phase protein, amyloidogenic protein, complement protein, and coagulation protein.

45. (New) The method according to claim 44, wherein the disease-associated protein is serum amyloid A protein (SAA).

46. (New) The method according to claim 44, wherein the disease-associated protein is serum amyloid P component (SAP).

47. (New) The method according to claim 44, wherein the disease-associated protein is an amyloidogenic protein selected from the group consisting of a monoclonal immunoglobulin light chain, transthyretin, β_2-microglobulin and lysozyme.